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Ottawa Hull K1A 0C9

(21) (A1) 2,123,242
(22) 1994/05/10
(43) 1994/11/12

(51) INTL.CL.[5] C07C-215/76; C07C-217/86; C07C-235/60; C07C-255/54; C07C-265/12; C07C-271/28

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Derivatives of 3-Fluorophenol, Processes for Preparing Them, and the Use of These Compounds

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(30) (DE) P 43 15 625.8 1993/05/11

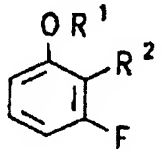
(57) 21 Claims

5,090,8/53

Abstract of the disclosure

Novel derivatives of 3-fluorophenol, processes for their preparation, and their use

The present invention relates to compounds of the formula (I)



(I)

in which R^1 is hydrogen, (C_1-C_8)-alkyl or CH_2-phenyl, where the alkyl radical or the phenyl group can be substituted by one to three (C_1-C_4)-alkoxy groups, fluorine, chlorine or bromine atoms, nitro groups, cyano groups, trifluoromethyl groups or (C_1-C_4)-alkoxycarbonyl groups, and R^2 is -CN, $-CONH_2$, $-NH_2$, -NCO or $-NHCOOR^3$, where R^3 has the meanings of R^1 other than that of hydrogen, and to a process for their preparation and to their use.

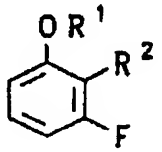
Description 2123242

Novel derivatives of 3-fluorophenol, processes for preparing them, and the use of these compounds

The present invention relates to novel derivatives of 3-fluorophenol, to processes for preparing them, and to the use of these compounds.

Derivatives of 3-fluorophenol are useful intermediates in the preparation of plant protection agents, pharmaceuticals and industrial products, such as, for example, liquid crystals. Owing to the general importance, and numerous uses, of this substance class, it represents a rewarding object to prepare novel compounds from this group of substances in order not only to supplement the spectrum of their possible applications, but also to enrich and extend it by giving nuances to material properties.

This object is achieved by compounds of the formula (I)



(I)

in which

R^1 is hydrogen, (C_1-C_8)-alkyl or CH_2-phenyl, where the alkyl radical or the phenyl group can be substituted by one to three (C_1-C_4)-alkoxy groups, fluorine, chlorine or bromine atoms, nitro groups, cyano groups, trifluoromethyl groups or (C_1-C_4)-alkoxycarbonyl groups, and

R^2 is $-CN$, $-CONH_2$, $-NH_2$, $-NCO$ or $-NHCOOR^3$, where R^3 has the meanings of R^1 other than that of hydrogen.

Cyclic, straight-chain or singly or multiply branched

alkyl radicals are generally suitable as alkyl radicals. Examples of such radicals are the methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, i-pentyl, n-hexyl, i-hexyl, n-heptyl, i-heptyl, n-octyl, i-octyl, 2-chloroethyl, 2-bromoethyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, 3-ethoxypropyl, 4-methoxybutyl, 3-chloropropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and methylcyclohexyl radicals.

In addition to unsubstituted phenyl, phenyl radicals which are substituted one to three times are generally suitable as phenyl radicals.

Those which may be mentioned here by way of example are 2-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 2,5-dichlorophenyl, 2,4-dichlorophenyl, 3-nitrophenyl, 4-cyanophenyl, 3,5-dimethoxyphenyl, 2-nitrophenyl and 2,4,5-trichlorophenyl.

R^1 is, in particular, hydrogen, a linear or branched (C_1-C_8)-alkyl group or a CH_2-phenyl group.

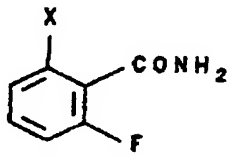
A certain importance is attached to the phenols of the formula I (R^1 = H) in which R^2 is $-CONH_2$ or NH_2, in particular 2-amino-3-fluorophenol and 2-hydroxy-6-fluorobenzamide.

The compounds of the formula I in which R^1 is CH_2-phenyl and R^2 is -CN, $-CONH_2$, NH_2 or $NHCOOR^3$, in particular 2-benzyloxy-6-fluorobenzamide, 2-benzyloxy-6-fluoroaniline, 2-benzyloxy-6-fluoro-N-benzyloxycarbonylaniline and 2-benzyloxy-6-fluorobenzonitrile, are also valuable intermediates.

The compounds of the formula I in which R^1 is (C_1-C_8)-alkyl and R^2 is -CN or $-CONH_2$, in particular 2-ethoxy-6-fluorobenzonitrile and 2-ethoxy-6-fluorobenzamide, are of interest.

The present invention additionally relates to processes for preparing the compounds according to the invention.

Thus, compounds of the formula I, in which R^1 is hydrogen, (C_1-C_8)-alkyl or CH_2-phenyl, where the alkyl radical or the phenyl group can be substituted by one to three (C_1-C_4)-alkoxy groups, fluorine, chlorine or bromine atoms, nitro groups, cyano groups, trifluoromethyl groups or (C_1-C_4)-alkoxycarbonyl groups, and R^2 is $-NH_2$ or $-NHCOOR^3$, can be prepared by reacting compounds of the formula (II)

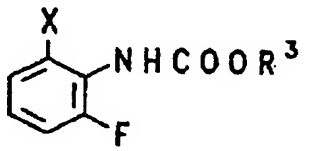


(II)

in which X is OR^1, in aqueous-alkaline medium, with chlorine, bromine, sodium hypochlorite or sodium hypobromite in the presence of alcohols and at temperatures of from -15°C to +80°C, in the sense of a Hofmann degradation.

In many cases, it has proved to be of value to employ, as the alcohol component, compounds of the formula HOR^3, where R^3 is (C_1-C_8)-alkyl or CH_2-phenyl, where the alkyl radical or the phenyl group can be substituted by one to three (C_1-C_4)-alkoxy groups, fluorine, chlorine or bromine atoms, nitro groups, cyano groups, trifluoromethyl groups or (C_1-C_4)-alkoxycarbonyl groups.

The compound of the formula (I')



(I')

resulting from the reaction can be isolated. However, it is also possible to cleave the carbamate group and/or, for X = OR^1, the group OR^1 (when R^1 is not hydrogen)

hydrogenolytically or hydrolytically without undertaking any intermediate isolation. It is likewise possible to select the reaction conditions such that the cleavage already takes place to a large extent at the same time as the rearrangement.

The compounds of the formula II are prepared by converting the corresponding nitriles into the benzamides by methods which are generally known in the literature (J. March, Advanced Organic Chemistry [1985], 788).

In this context, preference is given to the reaction of 2,6-difluorobenzonitrile in aqueous-alkaline medium with hydrogen peroxide (JP-OS 60-132 942), where appropriate in correspondance with the present invention, in the presence of from about 1 to about 20 mol, preferably from about 0.1 to 10 mol, particularly preferably between about 1.05 mol and 5 mol, of alcohol per 1 mol of 2,6-difluorobenzonitrile. In this context, alkan-(C_1-C_8)-ols of any structure, which can additionally be substituted by alkoxy(C_1-C_4) groups, fluorine, chlorine or bromine atoms, nitro groups, cyano groups, trifluoromethyl groups or alkoxy(C_1-C_4)-carbonyl groups, or phenylmethanols, where the phenyl radical can be substituted by alkyl(C_1-C_4) groups, alkoxy(C_1-C_4) groups, fluorine, chlorine or bromine atoms, nitro groups, cyano groups, trifluoromethyl groups or alkoxy(C_1-C_4)-carbonyl groups, can be used as R^1-OH alcohols; primary alcohols are preferred, with methanol, ethanol and benzyl alcohol being particularly preferred.

2,6-Difluorobenzamide can be isolated; however, it is also possible to obtain the compounds of the formula II having X = OR^1 immediately in a one-pot process. This can be achieved, in particular, by raising the reaction temperature.

The work is carried out at temperatures of between about 0° and about 90°C, preferably of between about 20° and

about 70°C.

If 2,6-difluorobenzamide, which has been isolated as an intermediate, is employed for preparing the compounds of the formula II having X = OR^1, the work is preferably carried out, in accordance with the invention, in excess alcohol, as described above, and reaction takes place, in the temperature range which has likewise already been defined, with about 1 mol to about 1.8 mol, particularly preferably with about 1.1 mol to about 1.5 mol, of alkali metal or alkaline earth metal compounds having an alkaline effect. Examples of such compounds having an alkaline effect are hydroxides, carbonates, hydrogen carbonates, phosphates, hydrogen phosphates, dihydrogen phosphates, oxides, or similar compounds, or mixtures thereof; sodium or potassium hydroxide or carbonate are preferred. The reaction times amount to from about 1 to about 16 h, with the reaction product generally being isolated, in the event that isolation is desired, by diluting the reaction mixture with water and filtering off (extraction, crystallization, chromatography).

Alternatively, it is possible to react 2,6-difluorobenzonitrile, as explained below, or 2,6-difluorobenzamide with the above-described quantities and types of compounds having an alkaline effect and alcohols in dipolar, aprotic solvents. Acetone, tetrahydrofuran (THF), acetonitrile, 1,2-dimethoxyethane (DMAc), N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP), dimethyl sulfoxide (DMSO), dimethyl sulfone, diphenyl sulfoxide, diphenyl sulfone, tetramethylurea, tetra-n-butylurea or 1,3-dimethylimidazolidin-2-one (DMI), or mixtures thereof, can be used as dipolar, aprotic solvents. Such solvents are used in quantities of about 50 to 500 % by mass, based on 2,6-difluorobenzamide or 2,6-difluorobenzonitrile, preferably in quantities of between about 80 and about 250 % by mass. The use of these solvents makes it possible to separate off by filtration the alkali metal or alkaline earth metal

fluoride which is formed in the reaction; the product is crystallized from the mother liquor by adding water and the solvent is recovered by distillation. In this variant of the process, the work is carried out at reaction temperatures of between about 30° and about 150°C, preferably of between about 40° and about 100°C. As compared with aqueous variants of the process, this variant has the advantage of higher yields.

The preparation of 2-(primary-alkoxy)-6-fluorobenzamides is preferred, with that of 2-methoxy-6-fluorobenzamide, 2-ethoxy-6-fluorobenzamide and 2-benzyloxy-6-fluorobenzamide being particularly preferred.

In the case of 2-benzyloxy-6-fluorobenzamide, 2-hydroxy-6-fluorobenzamide can be obtained by hydrogenolytic elimination of the benzyloxy group.

Compounds of the formula I ($R^1 \neq$ hydrogen) having $R^2 =$ CN can be obtained in an analogous manner. For this purpose, 2,6-difluorobenzonitrile is reacted with R^3OH alcohols in aqueous-alkaline or dipolar, aprotic medium in the presence of alkalis.

In this context, alkan-(C_1-C_8)-ols of any structure, which can additionally be substituted by alkoxy(C_1-C_4) groups, fluorine, chlorine or bromine atoms, nitro groups, cyano groups, trifluoromethyl groups or alkoxy-(C_1-C_4)-carbonyl groups, or phenylmethanols, where the phenyl radical can be substituted by alkyl(C_1-C_4) groups, alkoxy(C_1-C_4) groups, fluorine, chlorine or bromine atoms, nitro groups, cyano groups, trifluoromethyl groups or alkoxy-(C_1-C_4)-carbonyl groups, can be used as R^1-OH alcohols; primary alcohols are preferred, with methanol, ethanol and benzyl alcohol being particularly preferred.

It is also possible to obtain compounds of the formula I ($R^1 \neq$ hydrogen) having $R^2 = NH_2$ in a one-pot process by reacting either 2,6-difluorobenzonitrile or 2,6-difluoro-

benzamide in aqueous-alkaline medium with alcohols to form compounds of the formula II having X = OR^1 (R^1 ≠ hydrogen), and then reacting the latter, after intermediate isolation, but preferably without any intermediate isolation, in a one-pot process, with chlorine, bromine, sodium hypochlorite or sodium hypobromite, at temperatures of from -15°C to +80°C and in the presence of alcohols, in the sense of a Hofmann degradation, and subsequently, where appropriate, cleaving carbamates which have been formed hydrolytically or hydrogenolytically.

In this context, (C_1-C_8)-alkanols or phenylmethanols, where the alkyl radical or the phenyl radical can be substituted by one to three (C_1-C_4)-alkoxy groups, fluorine, chlorine or bromine atoms, nitro groups, cyano groups, trifluoromethyl groups or (C_1-C_4)-alkoxycarbonyl groups, in particular primary alcohols, can also be employed as alcohols.

In many cases, the use of methanol, ethanol or benzyl alcohol has proved to be advantageous.

These alcohols are employed in mixtures with aqueous solutions having an alkaline effect, as described above, preferably sodium or potassium hydroxide solutions. The compounds having an alkaline effect are used, dissolved or suspended in water, in quantities, based on the amide to be degraded, of between about 1 mol and about 30 mol, preferably of between about 3 mol and about 15 mol, particularly preferably of between about 5 mol and about 10 mol. While the concentrations of the aqueous solutions depend on the amide employed, the concentrations are typically between about 1 mol/l and about 20 mol/l, preferably between about 3 mol/l and about 10 mol/l. In practice, the quantity of the aqueous suspension having an alkaline effect is chosen such that it is still possible to stir the reaction mixture.

The procedure can be carried out using hypohalite solutions (bleaching liquors), which is completely equivalent to metering elemental halogen into solutions having an alkaline effect. An indication of the quantity of halogen employed is sufficient to describe the reaction conditions since, in situ, hypohalite solutions are formed when halogen makes contact with the aqueous solutions having an alkaline effect which are employed. Chlorine or bromine are used, therefore, in quantities of between about 1 mol and about 5 mol, preferably of from about 1.01 mol to about 2 mol, particularly preferably of between about 1.02 mol and about 1.2 mol, in each case based on 1 mol of amide to be degraded. Chlorine is preferably used since it is more readily available industrially. The halogen can be added dropwise (bromine) or passed in in gaseous form (chlorine). In this regard, suitable metering times on a laboratory scale are, depending on the reaction temperature, between about 0.5 h and about 8 h, preferably from about 1 h to about 4 h. Owing to the reaction being exothermic, the metering times on an industrial scale must be adapted to the cooling capacities available.

The reaction in the sense of the Hofmann degradation is carried out at temperatures of between about -15°C and about 100°C, preferably of between about 0°C and about 60°C, particularly preferably of between about 10°C and about 40°C.

If bleaching liquors, i.e. aqueous hypohalite solutions, are metered in, which generally has operational advantages as compared with the use of elemental halogen, solutions are then used having a content of active chlorine of from about 30 to about 250 g per kg of solution, preferably of between about 100 and about 160 g of active chlorine per kg of solution, or from about 60 to about 550 g of active bromine per kg of solution, preferably of between about 200 and about 350 g per kg of solution. These solutions may be obtained by metering the

corresponding quantities of chlorine or bromine into aqueous solutions having an alkaline effect.

In the variant according to the invention, the primary reaction product of the reaction in the sense of a Hofmann degradation is presumably the alkyl carbamate of the desired aniline, since the isocyanate arising as an intermediate is probably captured by the alcoholates, nucleophilic under the reaction conditions.

The anilines can be obtained from the carbamates by processes known in principle from the literature (T.W. Greene, P.G.M. Wuts, Protective Groups in Organic Chemistry (1991), 317-348). As a rule, liberation of the amino group is achieved by heating the reaction mixture according to the invention, once any excesses of chlorine or bromine have been destroyed. Optionally substituted benzyl carbamates can be hydrolyzed under alkaline conditions in less than 10 h at from 80 to 100°C, whereas simple alkyl carbamates require reaction times of up to 96 h at the same temperatures. The use of optionally substituted benzyl alcohol is therefore particularly preferred since the resulting benzyl carbamates can be cleaved without any great difficulty, and therefore cost-effectively, by hydrogenation (T.W. Greene et al., loc. cit., 335-341). The hydrogenolytic cleavage is preferably carried out in the presence of transition metal catalysts, in particular platinum, nickel or palladium catalysts. In general, the reaction products can be isolated simply by phase separation, resulting in mixtures with the alcohols employed. The phase separation can be improved or induced by adding additional solvents, such as, for example, toluene or xylene.

The resulting solutions of the free amines can, provided they contain compounds which possess benzyl groups, be hydrogenated by methods which are generally known from the literature (T.W. Greene et al., loc. cit., 47-68, 156-160, 335-341). Hydrogenation using hydrogen gas in

the presence of transition metal catalysts, preferably palladium catalysts, particularly preferably palladium on active charcoal, is preferred. An alternative option is to use the so-called transfer-hydrogenation method for synthesizing the novel intermediates (T.W. Greene et al., loc. cit., 156-160). Besides palladium, nickel or platinum, in particular, are suitable for employment as transition metals. The hydrogenations proceed smoothly under a hydrogen pressure of between about 1.1 bar and about 100 bar at temperatures of between about 10° and about 80°C in lower aliphatic alcohols or simple aromatic or aliphatic hydrocarbons, such as, for example, hexane, methylcyclohexane, toluene, xylene, methanol, butanol, isopropanol or ethanol as solvent, or mixtures thereof. The precious metal catalysts are employed in quantities of between about 0.05 and about 3, preferably of from about 0.3 to about 1, % by mass (calculated as pure transition metal). The concentration of the end product (in particular 2-amino-3-fluorophenol) in the hydrogenation mother liquor is typically between about 10 and about 500, preferably between about 100 and about 300, g/l. If the unsubstituted benzyl compounds are employed under these circumstances, the free hydroxyl groups and toluene are obtained during the hydrogenation. Toluene is therefore preferred as the solvent for the hydrogenation. The end product, 2-amino-3-fluorophenol, can be isolated by concentrating the solutions, from which, where appropriate, the catalyst has been filtered off while the solutions were hot, and subsequently filtering them. In this context, it is advisable to carry out the procedure in the presence of oxidation-preventing additives, such as hydrazine or hydrazinium salts, or 2,6-di-tert-butyl-4-methylphenol, since the end product exhibits a high degree of lability towards atmospheric oxygen, particularly on heating. Other phenol ether groupings, such as the methyl ethers or ethyl ethers which can preferably be prepared according to the invention, may be cleaved by methods known from the literature (T.W. Greene, loc. cit., 14.68, 145-161) before or after hydrogenating any

benzyl groups which may be present.

In the process according to the invention, the use of benzyl alcohol is particularly preferred in those reaction steps which proceed in the presence of alcohols.

6-Fluorosalicylamide can be prepared in high yield by cleaving the phenyl ether grouping in 2-alkoxy-6-fluorobenzamides by the methods which have already been described. The compound can be reacted, likewise in the described manner and optionally in the presence of alcohols, with halogens in alkaline solutions in the sense of a Hofmann degradation. Under these circumstances, the reaction proceeds as far as 2-amino-3-fluorophenol, as described above, provided that it involves formation of the carbamates. Otherwise, 6-fluorobenzoxazolone is obtained as an intermediate and has to be hydrolyzed in acid solution to yield the product, resulting in lower yields being obtained.

The compounds of the formula I, in particular compounds in which R^1 is hydrogen, methyl, ethyl or CH_2-phenyl, and R^2 is -CN, $-CONH_2$, $-NHCOOR^3$ or NH_2, with R^3 being methyl, ethyl or CH_2-phenyl, may be used for preparing liquid-crystalline compounds, plant protection agents and pharmaceuticals.

The following examples illustrate the invention without limiting it.

Example 1

2-Amino-3-fluorophenol

180 g of benzyl alcohol and 269 g (6.725 mol) of sodium hydroxide are introduced into 450 g of water. 220 g (0.9 mol) of 2-benzyloxy-6-fluorobenzamide are added at 20°C, and chlorine is passed in (15 l/h) at 40°C while stirring thoroughly. The reaction is monitored by gas

chromatography and terminated after 2.5 h when conversion is complete. The aqueous mother liquor is heated at 95°C for 3 h once any excess of chlorine has been destroyed (sodium sulfite).

At this point, 2-benzyloxy-6-fluoroaniline can be isolated as a pale-brown-colored viscous oil by extracting with MTBE, drying over magnesium sulfate and removing the solvent (see Example 3 as well); however, this step is omitted here.

Procedure a

The organic phase is separated from the aqueous phase, taken up in 200 ml of methanol, and then stirred vigorously (15 h) together with 5 g of Pd/C (5 % Pd, 50 % moist) under an H_2 atmosphere (slight excess pressure) until compounds possessing benzyloxy groupings can no longer be detected. The catalyst is filtered off and then washed with methanol. Most of the methanol is distilled off under an inert gas, and 300 g of toluene are added. After cooling (0°C), 60.9 g (0.48 mol, 53 %) of 2-amino-3-fluorophenol, which is colored pale-brown to dark-gray after drying, can be obtained (content (GC): 100 %). A further 24.2 g (0.19 mol, 21 %) of product are contained in the black mother liquor, as is determined by quantitative gas chromatography. The mother liquor is reused for further batches.

Procedure b

After some minutes without stirring, the phases can be separated after adding 200 g of toluene, and 300 g of methanol are added to the organic phase which is then stirred vigorously (20 h) together with 5 g of Pd/C (5 % Pd, 50 % moist) under an H_2 atmosphere (slight excess pressure). GC analysis reveals solvent and, apart from minor quantities of byproducts, 2-amino-3-fluorophenol, as the main component. The catalyst is filtered off and

then washed with methanol. Most of the methanol is distilled off from the filtrate under an inert gas, and 300 g of toluene are added. After cooling (0°C), and drying, 65.3 g (0.51 mol, 57 %) of 2-amino-3-fluorophenol, which is colored pale-brown, can be obtained (content (GC): 100 %). A further 28.2 g (0.22 mol, 25 %) of product are contained in the mother liquor, as was determined by quantitative gas chromatography. The mother liquor is reused for further batches.

2-Amino-3-fluorophenol:
M.p. 124-126°C; 126.3°C (DSC)
B.p. 250.7°C (DSC)
Solubility in water < 15 g/l
Bulk density approximately 0.2 g/cm^3

^{1}H-NMR [DMSO-d_6/TMS, ppm]:
δ = 6.39 (C) (ddd, 1H, J_{BC} = 8.28 Hz, J_{CD} = 6.36 Hz, J_{AC} = 7.83 Hz, Ar-H^5)
6.50 (B) (ddd, 1H, J_{BC} = 8.28 Hz, J_{BD} = 8.30 Hz, J_{AB} = 1.48 Hz, Ar-H^4)
6.52 (A) (ddd, 1H, J_{AC} = 7.83 Hz, J_{AD} = 2.30 Hz, J_{AB} = 1.48 Hz, Ar-H^6)

^{19}F-NMR [DMSO-d_6/$CFCl_3$, ppm]:
δ = -133.94 (D) (ddd, 1F, J_{BD} = 6.36 Hz, J_{AD} = 2.30 Hz, J_{CD} = 6.36 Hz, Ar-F^3)

^{13}C-NMR [DMSO-d_6/TMS, ppm]:
δ = 106.1 (J = 19.1 Hz, Ar-C^2), 110.5 (Ar-C^6), 115.4 (J = 9.4 Hz, Ar-C^1), 124.5 (J = 14.8 Hz, Ar-C^4) 146.1 (J = 7.9 Hz, Ar-C^5), 151.5 (J = -234.2 Hz, Ar-C^3)

MS: m/z (%) = 51 (14), 52 (16), 57 (2), 63 (3), 70 (6), 71 (7), 78 (7), 79 (13), 80 (5), 81 (4), 82 (8), 98 (57), 99 (5), 126 (11), 127 (100, M^+), 128 (7)

Example 2

A. Preparation of 2-benzyloxy-6-fluorobenzamide in aqueous medium

(1) 261.2 g (1.66 mol) of 2,6-difluorobenzamide are suspended in 232.3 g (2.15 mol) of benzyl alcohol, and the suspension is then heated to 55°C and 233.3 g (2.08 mol) of 50 % potassium hydroxide solution are added dropwise within the space of 2 h. At the end of this time, the temperature is raised to 60°C and the mixture is stirred for a further 3 h.

(2) The entire reaction mixture is allowed to flow, while stirring, into 1900 g of water, and the precipitated solid is filtered off with suction. Washing takes place 3 times with 200 ml of water on each occasion, and the product is dried at 70°C in vacuo. 297.7 g (1.21 mol, 73 %) of 2-benzyloxy-6-fluorobenzamide are obtained from 381 g of moist product as a slightly yellowish powder (purity (GC) > 98 %).

B. Preparation in dipolar, aprotic solvents

165.6 g (1.2 mol) of potassium carbonate are suspended in 230 g of N,N-dimethylacetamide (DMAc), and 113.4 g (1.05 mol) of benzyl alcohol are added to this suspension. After the addition of 157.1 g (1 mol) of 2,6-difluorobenzamide, the mixture is heated at 130°C for 24 h, and the fine salt which has precipitated is then filtered off and washed with 250 g of DMAc in several portions (184.5 g, dry). The organic phase (658.6 g) is added dropwise, while stirring, into 1100 g of water, resulting in the reaction product crystallizing out. Filtration takes place, and the filter cake is washed three times with 150 g of water on each occasion. 405 g of moist product are obtained as is, after drying, 170.7 g (0.696 mol, 70 %) of 2-benzyloxy-6-fluorobenzamide as a powder which is colored yellow-beige.

2-Benzyloxy-6-fluorobenzamide:
M.p. 142.6°C (DSC)

^{1}H-NMR [DMSO-d_6/TMS, ppm]:
δ = 5.15 (I) (s, 2H, Ar-CH_2)
6.81 (G) (ddd, 1H, J_{EG} = 8.2 Hz, J_{FG} = 0.5 Hz, J_{GK} = 8.9 Hz, Ar-H^5)
6.95 (F) (d(dd), 1H, J_{EF} = 8.5 Hz, J_{FG} = 0.5 Hz, J_{FK} = 0.5 Hz, Ar-H^3)
7.31 (H) (tm, 2H, Ar(benzyl)-$H^{3,5}$)
7.33 (E) (ddd, 1H, J_{EF} = 8.5 Hz, J_{EG} = 8.2 Hz, J_{EK} = -6.9 Hz, Ar-H^4)
7.38 (D) (tm, 1H, Ar(benzyl)-H^4)
7.45 (C) (dm, 2H, Ar(benzyl)-$H^{2,6}$)
7.49 (B) (s(br), 1H, Ar-$NH_2^{cis/trans}$)
7.80 (A) (s(br), 1H, Ar-$NH_2^{cis/trans}$)

^{19}F-NMR [DMSO-d_6/$CFCl_3$, ppm]:
δ = -116.40 (K) (ddd, 1F, J_{EK} = -6.9 Hz, J_{FK} = 0.5 Hz, J_{GK} = 8.9 Hz, Ar-F^6)

MS: m/z (%) = 63 (5), 65 (17), 91 (100), 92 (8), 98(3), 110 (6), 123 (4), 138 (3), 139 (5), 155 (1), 199 (1), 200 (1), 228 (20), 229 (3), 245 (8.1, M^+), 246 (1)

Example 3

2-Benzyloxy-6-fluoroaniline

120 g of methanol, 70 g of water, 30 g (0.75 mol) of sodium hydroxide and 24.5 g (0.1 mol) of 2-benzyloxy-6-fluorobenzamide are initially introduced and heated to 40°C. Chlorine is passed in (4 l/h), whereupon, after a short time, the colorless suspension assumes a slightly brownish color and the heating can be removed since the temperature is then maintained by the exothermic nature of the reaction. After 25 min, the reaction is complete, as can be demonstrated by GC. A clear solution is

obtained in place of the initial suspension. The methanol is distilled off (50°C) under a weak vacuum, and the resulting suspension of 2-benzyloxy-6-fluoro-N-carbomethoxyaniline is heated at 100°C for 48 h. After cooling, 50 g of toluene are added, the phases are separated, and 2 g of $MgSO_4$ and 1 g of active charcoal are added to the organic phase, which is stirred for some hours. After filtration and removal of the solvent on a rotary evaporator, 19.8 g (91 mmol, 91 %) of 2-benzyloxy-6-fluoroaniline are obtained as a brownish, clear oil, which exhibits a purity (GC: > 95 %) which is excellent for subsequent reactions.

2-Benzyloxy-6-fluoroaniline:
^{1}H-NMR [DMSO-d_6/TMS, ppm]:
δ = 4.57 (H) (s(br), 2H, Ar-NH_2)
5.13 (G) (s, 2H, Ar(benzyl)-CH_2)
6.51 (F) (ddd, 1H, J_{EF} = 8.35 Hz, J_{DF} = 8.15 Hz, J_{IF} = 6.35 Hz, Ar-H^4)
6.68 (E) (ddd, 1H, J_{EF} = 8.35 Hz, J_{DE} = 1.30 Hz, J_{EI} = 10.6 Hz, Ar-H^5)
6.77 (D) (ddd, 1H, J_{ED} = 1.30 Hz, J_{DF} = 8.15 Hz, J_{DI} = 1.20 Hz, Ar-H^3)
7.21 (C) (tm, 1H, Ar(benzyl)-H^4)
7.39 (C) (tm, 2H, Ar(benzyl)-$H^{3,5}$)
7.48 (B) (dm, 2H, Ar(benzyl)-$H^{2,6}$)

^{19}F-NMR [DMSO-d_6/$CFCl_3$, ppm]:
δ = -133.77 (I) (ddd, 1F, J_{EI} = 10.6 Hz, J_{FI} = 6.35 Hz, J_{DI} = 1.20 Hz, Ar-F^6)

MS: m/z (%) = 51 (9), 63 (4), 65 (16), 91 (100), 92 (8), 98 (16), 126 (10), 138 (0.5), 217 (17.6, M^+), 218 (2.6)

2-Benzyloxy-6-fluoro-N-carbomethoxyaniline can be isolated if the procedure indicated above is followed but the 48-hour long hydrolysis of the intermediate is omitted and the latter is isolated and purified in

accordance with customary methods (in particular filtration and recrystallization).

MS: m/z (%) = 51 (3.2), 59 (1.7), 63 (3.0), 65 (14.0), 70 (3.2), 83 (1.6), 89 (2.5), 91 (100), 92 (9.7), 112 (1.2), 152 (1.6), 153 (1.3), 216 (1.6), 243 (8.0), 244 (1.3), 275 (15.0, M^+), 276 (2.6)

2-Benzyloxy-6-fluorophenyl isocyanate arises as an intermediate in the synthesis and can be isolated if so desired.

MS: m/z (%) = 51 (4.2), 63 (3.1), 65 (15.1), 76 (5.3), 89 (3.2), 91 (100), 92 (8.2), 96 (2.6), 108 (1.1), 152 (8.9), 124 (3.7), 152 (1.6), 243 (15.9, M^+)

Example 4

2-Ethoxy-6-fluorobenzamide

69.6 g (0.5 mol) of 2,6-difluorobenzonitrile and 237 g (2 mol) of 6-normal sodium hydroxide solution are initially introduced in 270 ml of ethanol. 221 g (1.95 mol) of 30 % hydrogen peroxide solution are added dropwise to this mixture within the space of 30 min, during which the temperature, which was 20°C at the beginning of the addition, rises to 50°C and is then maintained at this value. After 5 h, the mixture is cooled and the precipitated white solid is filtered off with suction (19.2 g, m.p. 187.8°C). The latter is recrystallized from aqueous ethanol, yielding 16.5 g (90 mmol, 18 %) of pure, colorless 2-ethoxy-6-fluorobenzamide. 18.6 g (0.118 mol, 24 %) of 2,6-difluorobenzamide can additionally be isolated from the mother liquor by distilling off 62 g of ethanol, and a further 17.5 g of this compound can be obtained in impure form (purity about 60 %) by extracting the mother liquor with

dichloromethane and removing the solvent.

2-Ethoxy-6-fluorobenzamide:
M.p. 195.5°C (DSC)

^{19}F-NMR [DMSO-d_6/$CFCl_3$, ppm]:
δ = -115.98 (D) (ddd, 1F, J_{AD} = 6.65 Hz, J_{CD} = 9.07 Hz, J_{BD} = 0.70 Hz, Ar-F^6)

MS (EI, 70 eV): m/z (%) = 40 (3), 44 (8), 57 (9), 63 (5), 74 (2), 82 (9), 83 (17), 98 (4), 110 (48), 111 (4), 123 (34), 124 (3), 138 (100), 139 (32), 140 (4), 151 (16), 166 (39), 168 (37), 169 (3), 183 (4.5, M^+)

^{1}H-NMR [Acetone-d_6/TMS, ppm]:
δ = 1.36 (t, 3H, $-CH_2-CH_3$)
4.12 (qu, 2H, $-CH_2-CH_3$)
6.7 (s(br), 1H, Ar-$NH_2^{cis/trans}$)
6.71 (C) (ddd, 1H, J_{AC} = 8.4 Hz, J_{BC} = 0.78 Hz, J_{CD} = 9.07 Hz, Ar-H^4)
6.84 (B) (ddd, 1H, J_{BC} = 0.78 Hz, J_{AB} = 8.4 Hz, J_{BD} = 0.70 Hz, Ar-H^5)
6.9 (s(br), 1H, Ar-$NH_2^{cis/trans}$)
7.31 (A) (ddd, 1H, J_{AD} = 6.65 Hz, J_{AB} = 8.4 Hz, J_{AC} = 8.4 Hz, Ar-H^3)

IR (KBr, cm^{-1}): 3375, 3190, 2990 (w), 2985 (w), 2940 (w), 1650, 1570, 1490, 1460, 1400, 1390, 1270, 1240, 1115, 1060, 1000, 810, 785, 755, 700, 645, 620, 530, 420

Example 5

2-Benzyloxy-6-fluorobenzonitrile

100 g of benzyl alcohol and 55.6 g (0.4 mol) of 2,6-difluorobenzonitrile are initially introduced and heated to 40°C. 49.2 g (0.44 mol) of 50 % potassium hydroxide

solution are then added dropwise, with stirring, in such a way that the temperature can be maintained (cooling).

After 4 h, the mixture is diluted with 200 ml of water, the precipitated product is filtered off with suction, and 50 g of toluene are added to the mother liquor in a separating funnel. The yield of moist product is 62.0 g, and, after drying, 56.2 g (0.247 mol, 62 %) of 2-benzyloxy-6-fluorobenzonitrile (purity (GC) 99.3 %) remain in the form of a slightly yellowish solid. 31.5 g of 92.4 % pure material (29.1 g, 0.128 mol, 32 %) are obtained from the organic phase by removing the toluene in vacuo (up to 190°C). After dissolving the crude products in ethanol/water and crystallizing without filtration, the yield of pure 2-benzyloxy-6-fluorobenzonitrile is 81.2 g (0.36 mol, 90 %); the product is obtained in the form of colorless shiny platelets.

2-Benzyloxy-6-fluorobenzonitrile
M.p. 71.9°C (DSC)

MS: m/z (%) = 50 (3), 51 (6), 57 (3), 63 (7), 65 (27), 89 (5), 91 (100), 92 (15), 108 (7), 120 (1), 136 (1), 170 (1), 227 (M^+, 13.7), 228 (2.4)

Example 6

6-Fluorosalicylamide

24.3 g (0.1 mol) of 2-benzyloxy-6-fluorobenzamide are stirred vigorously (16 h), at 20°C and under an H_2 atmosphere (slight excess pressure), in 150 g of toluene together with 5 g of Pd/C (5 %, 50 % moist). After that, only the desired salicylamide can be detected in the mixture. The catalyst is filtered off and then washed with 100 ml of methanol in several portions in order to dissolve off undissolved product from the solid. The filtrate is concentrated (about 150 g) under a weak

vacuum, and then cooled down to 0°C, whereupon colorless crystals of 2-hydroxy-6-fluorobenzamide precipitate out. These latter are filtered off with suction and washed with cold toluene and hexane. After drying, 14.2 g (91.5 mmol, 92 %) of colorless 6-fluorosalicylamide are obtained.

2-Hydroxy-6-fluorobenzamide (6-fluorosalicylamide)
M.p. 144-146.5°C

MS: m/z (%) = 44 (14), 57 (20), 63 (19), 71 (5), 81 (12), 82 (24), 83 (25), 98 (5), 110 (100), 111 (11), 113 (8), 138 (80), 139 (19), 141 (19), 155 (74.4, M^+), 156 (6.4), 157 (11.5)

Example 7

2-Amino-3-fluorophenol via 2-hydroxy-6-fluorobenzamide (6-fluorosalicylamide)

15.5 g (0.1 mol) of 6-fluorosalicylamide are introduced into 100 g of 30 % sodium hydroxide solution, and chlorine is passed (4 l/h) into the resulting clear solution. After 30 min, the chlorine stream is shut off, and excess chlorine is destroyed (sodium sulfite). The pH of the solution is adjusted to 6 with sulfuric acid and the precipitated 3-fluorobenzoxazolone is filtered off with suction at 0°C. The moist product (16.6 g) is heated at 130°C for 3 h in 80 g of 70 % sulfuric acid, and, after cooling, the pH of the mixture is once again adjusted to 6, and filtration with suction takes place at 0°C. 7.3 g (57 mmol, 57 %) of dark-gray 2-amino-3-fluorophenol are obtained with a purity of 98 % (GC); the black mother liquor is discarded.

2-Hydroxy-6-fluoro-N-carbomethoxyaniline, inter alia, is formed if a little methanol is added to the reaction mixture.

MS: m/z (%) = 51 (19.7), 59 (18.8), 70 (15.4), 71 (11.0), 97 (13.1), 98 (69.2), 109 (6.3), 126 (100), 127 (8.4), 140 (5.9), 153 (32.4), 154 (5.3), 185 (71.1, M^+), 186 (6.4)

Example 8

2-Amino-3-fluorophenol in a one-pot process starting from 2,6-difluorobenzamide

The procedure described in Example 2A. (1) is carried out. After that, a further 600 g of water, 280 g (7 mol) of sodium hydroxide and 185 g (1.71 mol) of benzyl alcohol are added at 10°C, and chlorine is passed in (15-18 l/h) at 40°C for 3 h. The phases are separated, and 500 ml of methanol and 7 g of Pd/C (5 %, 50 % moist) are added to the organic phase and hydrogenation is carried out as described in Example 1b. After working up in analogy to Example 1b, 123.5 g (0.97 mol, 59 %) of 2-amino-3-fluorophenol are obtained as pale-gray shiny platelets.

Example 9

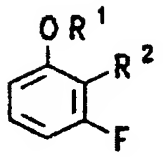
2-Amino-3-fluorophenol in a one-pot process starting from 2,6-difluorobenzonitrile

69.6 g (0.5 mol) of 2,6-difluorobenzonitrile and 237 g (1.2 mol) of 6-normal sodium hydroxide solution are initially introduced in 200 ml of benzyl alcohol. 221 g (1.95 mol) of 30 % hydrogen peroxide solution are added dropwise to this mixture within the space of 30 min, during which the temperature, which was 20°C at the beginning of the addition, rises to 50°C and is then maintained at this value. After 5 h (complete conversion to 2-benzyloxy-6-fluorobenzamide can be detected by means of GC), the mixture is cooled down and supplemented with 200 g of water and 60 g (1.5 mol) of sodium hydroxide.

Chlorine is passed in (8-10 l/h) at 30°C for 2 h, with the reaction being monitored by gas chromatography and terminated when the amide has disappeared. The phases are separated, and 180 g of methanol are added to the organic phase, and this is followed by further working up as indicated in Example 8. 32.4 g (0.255 mol, 51 %) of 2-amino-3-fluorophenol are obtained as a brown-black powder.

Patent claims:

1. A compound of the formula (I)



(I)

in which R^1 is hydrogen, (C_1-C_8)-alkyl or CH_2-phenyl, where the alkyl radical or the phenyl group can be substituted by one to three (C_1-C_4)-alkoxy groups, fluorine, chlorine or bromine atoms, nitro groups, cyano groups, trifluoromethyl groups or (C_1-C_4)-alkoxycarbonyl groups, and R^2 is -CN, $-CONH_2$, $-NH_2$, -NCO or $-NHCOOR^3$, where R^3 has the meanings of R^1 other than that of hydrogen.

2. A compound as claimed in claim 1, wherein R^1 is hydrogen, (C_1-C_8)-alkyl or CH_2-phenyl, R^2 is -CN, $-CONH_2$, $-NH_2$, -NCO or $-NHCOOR^3$, and R^3 is (C_1-C_8)-alkyl or CH_2-phenyl.

3. A compound as claimed in claim 1 or 2, wherein R^1 is hydrogen and R^2 has the meaning as claimed in claim 1, preferably $-CONH_2$, or $-NH_2$.

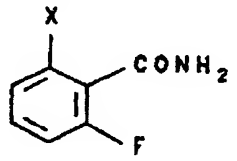
4. A compound as claimed in claim 1 or 2, wherein R^1 is CH_2-phenyl and R^2 has the meaning as claimed in claim 1, preferably -CN, $-CONH_2$, $-NH_2$ or $-NHCOOR^3$.

5. A compound as claimed in claim 1 or 2, wherein R^1 is (C_1-C_8)-alkyl and R^2 has the meaning as claimed in claim 1, preferably -CN or $-CONH_2$.

6. A compound of the formula (I) as claimed in claim 1 from the group comprising 2-amino-3-fluorophenol, 2-hydroxy-6-fluorobenzamide, 2-benzyloxy-6-fluorobenzamide, 2-benzyloxy-6-fluoroaniline, 2-benzyloxy-6-fluoro-N-benzyloxycarbonylaniline,

2-benzyloxy-6-fluorobenzonitrile, 2-ethoxy-6-fluorobenzonitrile and 2-ethoxy-6-fluorobenzamide.

7. A process for preparing compounds of the formula (I) as claimed in claim 1, in which R^1 has the meaning as claimed in claim 1 and R^2 is $-NH_2$ or $-NHCOOR^3$, wherein compounds of the formula (II)

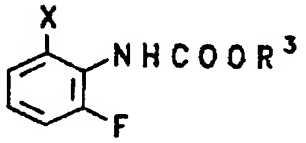


(II)

in which X is OR^1, are reacted, in aqueous-alkaline medium, with chlorine, bromine, sodium hypochlorite or sodium hypobromite in the presence of alcohols and at temperatures of from -15°C to +80°C, in the sense of a Hofmann degradation.

8. The process as claimed in claim 7, wherein the reaction is effected in the presence of an alcohol, HOR^3, where R^3 has the same meaning as in claim 1.

9. The process as claimed in claim 8, wherein the compound of the formula (I')



(I')

resulting therefrom is either isolated, or the carbamate group and/or, for X = OR^1, the group OR^1 (when R^1 is not hydrogen) is cleaved hydrogenolytically or hydrolytically.

10. The process as claimed in at least one of claims 7 to 9, wherein 2,6-difluorobenzonitrile is used as the starting compound for preparing the compounds (II) and the nitrile group is converted, in a manner known per se, into the amide group, and, in the case

of compounds in which X is OR^1, the corresponding F atom is replaced by the OR^1 group before, during or after this conversion.

11. The process as claimed in claim 10, wherein the replacement of the fluorine atom by an alkoxy group is effected at the same time as the conversion of the nitrile group into the amide group in such a way that the 2,6-difluorobenzonitrile is converted, in the presence of an alcohol, HOR^3, where R^3 has the same meaning as in claim 1 and preferably represents benzyl, into the corresponding benzamide, and the OR^1 group (here R^1 is different from hydrogen) is subsequently, where appropriate, cleaved hydrogenolytically.

12. The process as claimed in claim 10, wherein the 2,6-difluorobenzonitrile for preparing the compound of the formula (I) having R^2 = CN is reacted with an alcohol, HOR^3, where R^3 possesses the same meaning as in claim 1, in aqueous-alkaline medium or in a dipolar, aprotic solvent in the presence of alkalis.

13. A process for preparing the compounds of the formula (I) as claimed in claim 1, in which R^2 is NH_2, wherein either 2,6-difluorobenzonitrile or 2,6-difluorobenzamide is reacted, in aqueous-alkaline medium, with alcohols to form compounds of the formula II having X = OR^1, and these latter are then, after intermediate isolation, but preferably without any intermediate isolation, reacted, in a one-pot process, with chlorine, bromine, sodium hypochlorite or sodium hypobromite, at temperatures of from -15°C to +80°C and in the presence of alcohols, in the sense of a Hofmann degradation, and, where appropriate, carbamates which have been formed are subsequently cleaved hydrolytically or hydrogenolytically.

14. The process as claimed in claim 13, wherein (C_1-C_8)-alkanols or phenylmethanols, where the alkyl radical or the phenyl radical can be substituted by one to three (C_1-C_4)-alkoxy groups, fluorine, chlorine or bromine atoms, nitro groups, cyano groups, trifluoromethyl groups or (C_1-C_4)-alkoxycarbonyl groups, in particular primary alcohols, are employed as alcohols.

15. The process as claimed in claim 13 or 14, wherein the alcohols are methanol, ethanol or benzyl alcohol.

16. The process as claimed in at least one of claims 13 to 15, wherein the reactions to form the 2-alkoxy-6-fluorobenzamides are carried out in aqueous-alkaline medium or in one or more dipolar, aprotic solvents in the presence of alkalis.

17. The process as claimed in at least one of claims 13 to 15, wherein the reaction to form the compounds of the formula (II) having X = OR^1 is effected at temperatures of from 0°C to 90°C, preferably of from 20°C to 70°C.

18. The process as claimed in claim 16, wherein the reaction is effected at temperatures of from 30°C to 150°C, preferably of from 40°C to 100°C.

19. The process as claimed in at least one of claims 13 to 18, wherein the carbamate groups, and, where appropriate, the OR^1 groups as well, contained in the compounds obtained by the Hofmann degradation, are cleaved hydrogenolytically and/or hydrolytically.

20. The process as claimed in claim 19, wherein the hydrogenolytic cleavage is carried out in the presence of transition metal catalysts, in

particular platinum, nickel or palladium catalysts.

21. Use of the compounds of the formula (I), as claimed in claim 1, in particular compounds in which R^1 is hydrogen, methyl, ethyl or CH_2-phenyl, and R^2 is -CN, $-CONH_2$, $-NH_2$ or $-NHCOOR^3$, with R^3 being methyl, ethyl or CH_2-phenyl, for preparing liquid-crystalline compounds, plant protection agents or pharmaceuticals.

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REMPLACEMENT

SECTION is not Present

Cette Section est Absente